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Left Ventricular Diastolic Filling Abnormalities Identified by Doppler Echocardiography in Asymptomatic Patients With Sickle Cell Anemia

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To determine whether left ventricular diastolic abnormalities are an early feature of sickle cell anemia, indexes of diastolic filling were obtained with pulsed Doppler echocardiography in 30 consecutive patients with this disease (mean age 29 years; range 19 to 39) who had not experienced symptoms of heart failure and had normal left ventricular systolic function. Data were compared with those in 30 normal control subjects of similar ages.

Seventeen (57%) of the 30 patients with sickle cell anemia had evidence of abnormal left ventricular diastolic filling. Six of these 17 patients had a Doppler pattern consistent with "restrictive" filling, characterized by reduced early diastolic deceleration time (<110 ms) or an increased rate of decline of early flow velocity (EF slope >7.4 m/s^2), or both, as well as decreased late diastolic velocity-time integral (2.6 ± 0.7 vs. 3.4 ± 0.8 cm in normal subjects; $p < 0.05$). Another 11 patients showed a Doppler waveform consistent with impaired relaxation, characterized by prolonged deceleration time (>166 ms) or reduced EF slope (<3.8 m/s^2), as well as increased late diastolic velocity-time integral (4.0 ± 0.5 vs. 3.4 ± 0.8 cm in normal subjects; $p = 0.03$).

This Doppler echocardiographic analysis demonstrates that left ventricular diastolic filling patterns are altered in patients with sickle cell anemia and that these diastolic abnormalities may be present in the absence of symptoms of heart failure. These abnormal patterns suggest an intrinsic myocardial abnormality in patients with sickle anemia and may prove to be early markers of cardiac disease.

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Patients with sickle cell anemia, a hereditary hemoglobinopathy, often have signs or symptoms of congestive heart failure (1–6). This clinical observation has prompted the hypothesis that an intrinsic myocardial abnormality is part of the sickle cell disease process (7,8). However, because previous investigations have failed to demonstrate convincingly major impairment of left ventricular systolic performance in patients with sickle cell anemia (9–14), it has been suggested that diastolic abnormalities may be an important component of this disease (15). The present Doppler echocardiographic study was undertaken to determine systematically whether patients with sickle cell anemia have left ventricular diastolic abnormalities that can serve as subclinical markers of cardiac disease.

Methods

Selection of patients. Patients evaluated in the Howard University Sickle Cell Anemia Clinic were prospectively screened from October 1988 to March 1989. Thirty patients who met the following criteria were included in the study: 1) age <40 years; 2) absence of cardiac symptoms or clinical evidence of heart disease; 3) normal left ventricular systolic performance (systolic fractional shortening ≥30% and no segmental wall motion abnormalities on two-dimensional echocardiography); 4) no clinical or echocardiographic evidence of pulmonary hypertension or right ventricular systolic dysfunction, and 5) absence of sickle cell crisis or blood transfusion in the 3 months preceding echocardiographic study. Systemic blood pressure was normal in each patient at the time of the study and no patient was taking cardioactive medications. The study protocol was reviewed and approved by the Howard University Institutional Review Board and written informed consent was provided by each patient.

Study patients. The 30 patients, 15 men and 15 women, ranged in age from 19 to 39 years (mean 30). Twenty-three patients (77%) had the homozygous form of sickle cell anemia (hemoglobin SS); the remaining 7 had the heterozygous form (hemoglobin SC). Hemoglobin level ranged from 8.5 to 12.7 g/dl (mean 9.2). Twenty-nine of the 30 patients had received <10 blood transfusions (mean 2); the remaining patient had received 54.

A control group of 30 volunteer subjects of similar age, but without clinical or echocardiographic evidence of cardiovascular disease, was studied for comparison. Control

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subjects ranged in age from 23 to 38 years (mean 29); 20 were male and 10 were female.

Echocardiography. Two-dimensional echocardiography was performed using a phased array imaging system (Hewlett-Packard model 77020AC) with a 2.5 MHz transducer. Images of the heart were obtained in multiple cross-sectional planes with use of standard transducer positions (16) and were recorded on 0.5 in. (1.27 cm) videotape for subsequent review and analysis. M-mode echocardiograms were derived from the two-dimensional images under direct anatomic visualization and were recorded with a strip chart recorder at 50 mm/s. Cardiac dimensions were measured according to the recommendations of the American Society of Echocardiography (17). Left ventricular mass was calculated with the formula of Devereux et al. (18), which makes appropriate corrections for measurements obtained with use of American Society of Echocardiography conventions. Mass index was calculated by dividing the left ventricular mass by body surface area.

Doppler echocardiography. Each subject was examined by Doppler echocardiography in the left lateral decubitus position with the transducer at or slightly to the left of the apical impulse. The transducer was oriented to obtain an apical four-chamber view of the heart that provided visualization of the left ventricular cavity and maximal excursion of the mitral valve leaflets. The Doppler cursor line was then positioned through a plane traversing the left ventricle from apex to mitral anulus, taking care to attain the smallest possible angle between the presumed direction of diastolic transmitral blood flow and the ultrasound beam (cursor); this angle was estimated to be <20° in each subject. The Doppler sample volume was positioned in the inflow area of the left ventricle between the mitral leaflets, and the area was interrogated to obtain waveforms with the highest peaks of diastolic flow velocity and the optimal signal to noise ratio; these were usually identified within the left ventricular cavity about 1 cm below the mitral anulus, near the tips of the mitral leaflets.

Doppler waveforms were recorded with a simultaneous lead II electrocardiogram (ECG) and phonocardiogram on a strip chart at 100 mm/s paper speed. In each subject, three to five consecutive cardiac cycles were chosen for analysis. Left ventricular diastolic flow velocity waveforms from these cardiac cycles were measured and the values averaged. Doppler tracings from patients and control subjects were coded and measurements were obtained by one observer who had no knowledge of the identity of the subjects.

The following Doppler indexes of diastolic filling were obtained in each subject: 1) time interval from the aortic closing component of the second heart sound to the onset of diastolic flow velocity (A_2D), a measure of the duration of isovolumic relaxation; 2) early diastolic peak flow velocity measured as the height of the early peak of flow velocity (E); 3) rate of decline of flow velocity in early diastole (EF slope); 4) deceleration time of early diastolic flow velocity measured as the time interval between the early peak of flow velocity and the intersection of the EF slope with baseline; 5) peak flow velocity during atrial contraction measured as the height of the late diastolic peak (A); and 6) the ratio between the maximal early and late diastolic flow velocities (E/A). These Doppler diastolic indexes have been previously shown to have satisfactory reproducibility (19). In addition, the transmitral waveforms were digitized along the darkest lines of the velocity spectra (modal velocity) with use of the computer software incorporated into the Hewlett-Packard imaging system. Velocity-time integrals of the early diastolic (E) and late diastolic (A) components, total transmitral flow velocity and the ratio of late diastolic to total transmitral integral (a measure of atrial contribution to total filling) were calculated. No patient had clinical or Doppler echocardiographic evidence of mitral regurgitation.

Table 1. Left Ventricular Dimensions in 30 Patients With Sickle Cell Anemia and 30 Normal Control Subjects*

	Sickle Cell Anemia	Normal Control Subjects	p Value
RR interval (ms)	841 ± 96	864 ± 110	NS
Systolic BP (mm Hg)	114 ± 17	124 ± 12	0.04
LV diastolic dimension (mm)	55 ± 6.4	50 ± 4.1	< 0.01
Septal thickness (mm)	9.5 ± 1.5	9.1 ± 1.2	NS
Posterior wall thickness (mm)	9.2 ± 1.6	8.7 ± 1.4	NS
Left atrial size (mm)	38 ± 4.8	35 ± 3.2	< 0.01
LV mass (g)	168 ± 55	136 ± 39	< 0.01
LV mass index (g/m²)	93 ± 26	76 ± 18	< 0.01
% Fractional shortening	36 ± 4	38 ± 4	NS

*Values are expressed as mean values ± SD. BP = blood pressure; LV = left ventricular.

Statistical methods. Data are expressed as mean values ± SD. Mean differences in Doppler indexes between patients and control subjects were analyzed by using the unpaired Student's *t* test. In the individual patient analysis, diastolic filling patterns were judged to be abnormal if one or more Doppler indexes were outside the 95% confidence tolerance limits obtained from data in the 30 normal control subjects. Differences among subgroups of patients with sickle cell anemia were assessed with one-way analysis of variance.

Results

Left ventricular dimensions (Table 1). Ventricular septal and posterior free wall thicknesses were normal and did not differ significantly between patients with sickle cell anemia and control subjects. However, left ventricular transverse end-diastolic dimension was greater in patients with sickle cell anemia (55 ± 6 mm vs. 50 ± 4 mm; $p < 0.01$) and was increased in absolute terms (>95% confidence tolerance limits) in 14 of the 30 patients (range 56 to 66 mm). As a consequence of the increased diastolic dimension, calculated left ventricular mass and mass index were also increased in

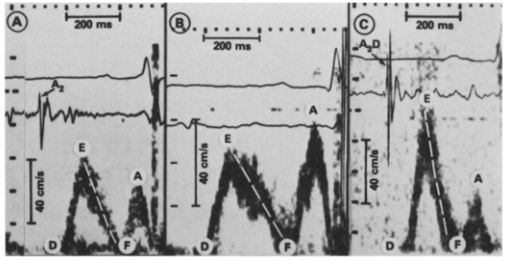

Figure 1. Spectrum of transmitral diastolic flow velocity waveforms obtained with pulsed Doppler echocardiography in three patients with sickle cell anemia. **A,** Normal diastolic waveform. Each index of diastolic filling is within the normal limits established from values in control subjects. A = late diastolic peak flow velocity; A_2D = isovolumic relaxation time; E = early diastolic peak flow velocity; EF = rate of decline of flow velocity in early diastole. Deceleration time was measured as the time interval between the early diastolic peak flow velocity (E) and the intersection of the EF slope with the baseline. **B,** impaired relaxation pattern. Rate of decrease of flow velocity in early diastole is slowed as evidenced by an increased deceleration time (240 ms) and a reduced EF slope (1.7 m/s^2) compared with that of the normal waveform shown in **panel A. C,** restrictive filling pattern. Abnormally rapid and abrupt decrease in left ventricular filling in early diastole, as evidenced by the shortened deceleration time (90 ms) and increased EF slope (8.7 m/s^2) compared with the normal waveform **(A)** and the abnormal waveform of impaired relaxation **(B).** Each vertical division represents a 20 cm/s increment in flow velocity; horizontal time-line divisions are 40 ms apart. In each panel the **top tracing** is an ECG and the **middle tracing** is a phonocardiogram.

the patients with sickle cell anemia compared with control subjects (Table 1).

Patterns of Left Ventricular Diastolic Filling (Fig. 1, Table 2)

A spectrum of left ventricular diastolic filling patterns was observed in patients with sickle cell anemia. Seventeen (57%) of the 30 patients had evidence of abnormal early diastolic filling.

Restrictive filling pattern. Six of these 17 patients showed a pattern consistent with "restrictive" filling (20) and characterized by abrupt and premature decrease in early diastolic flow velocity, as evidenced by a shortened deceleration time (<110 ms) or an accelerated rate of decline of flow velocity (EF slope >7.4 m/s^2) or both. In these six patients there was no difference in early diastolic velocity-time integral compared with that in normal subjects; however, the late diastolic velocity-time integral was smaller in patients with sickle cell anemia than in the normal subjects (2.6 ± 0.7 vs. 3.4 ± 0.8; $p < 0.05$). The ratio of late diastolic to total velocity-time integral (a measure of the contribution of late diastolic flow velocity to the total) was less in patients with sickle cell anemia than in control subjects (0.25 ± 0.02 vs. 0.30 ± 0.06), but this difference did not achieve statistical significance ($p = 0.06$). In addition, four of these six patients had other abnormal Doppler indexes, including increased early diastolic peak flow velocity in two and shortened isovolumic relaxation time in two others.

Impaired relaxation pattern. Eleven other patients showed a Doppler pattern consistent with impaired left ventricular relaxation and characterized by abnormally delayed early diastolic filling, as evidenced by increased deceleration time (>166 ms) or a decreased rate of decline of flow velocity in early diastole (EF slope <3.8 m/s^2) or both. The late diastolic velocity-time integral in these 11 patients was increased compared with that in normal subjects (4.0 ± 0.5 vs. 3.4 ± 0.8 cm; $p = 0.03$). However, the early diastolic velocity-time integral did not differ between these 11 patients and the normal subjects. In addition, seven of these patients had other abnormal Doppler indexes, including decreased early diastolic peak flow velocity in three, increased late diastolic peak flow velocity in one and prolonged isovolumic relaxation time in three. The ratio of the early to late diastolic peaks of flow velocity was normal in each of these 11 patients.

The remaining 13 patients with sickle cell anemia showed normal transmitral flow velocity waveforms in which each index of diastolic filling was within the 95% confidence

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Table 2. Doppler-Derived Indexes of Left Ventricular Diastolic Filling in 17 Patients With Sickle Cell Anemia

	DT (ms)	EF Slope (m/s^2)	VTI-E (cm)	VTI-A (cm)	AFF	E (cm/s)	A (cm/s)	E/A	A_2D (ms)
Normal limits*	110, 166	3.8, 7.4	5.7, 9.7	2.2, 4.6	0.22, 0.39	53, 86	27, 59	0.7, 2.8	61, 87
Restrictive filling (6 patients)									
1	90†	9.0†	8.6	2.7	0.21†	90†	39	2.3	70
2	90†	7.5†	6.2	3.0	0.33	71	42	1.7	78
3	105†	7.3	6.9	2.0†	0.22	78	42	1.9	50†
4	105†	6.3	8.1	3.2	0.29	80	48	1.7	80
5	107†	8.7†	9.6	3.3	0.26	93†	50	1.9	80
6	140	8.2†	6.8	1.7†	0.19†	67	38	1.8	55†
Impaired relaxation (11 patients)									
1	235†	1.9†	7.5	4.8†	0.41†	42†	52	0.8	53
2	206†	4.4	15.8†	3.3	0.17	102†	38	2.7	43
3	185†	4.1	8.4	4.7†	0.35	72	59	1.2	90†
4	175†	3.7†	9.0	3.9	0.39	65	39	1.7	91†
5	175†	4.0	9.7	4.3	0.31	75	50	1.5	70
6	170†	3.3†	6.1	4.0	0.41†	53	65†	0.8	75
7	170†	3.7†	7.3	4.1	0.35†	59	45	1.3	90†
8	170†	4.1	9.4	4.4	0.32	72	53	1.4	83
9	169†	4.0	7.3	3.1	0.30	62	54	1.1	63
10	165	2.8†	6.8	3.8	0.33	42†	40	1.1	65
11	135	3.5†	4.6†	3.6	0.45†	50†	35	1.4	55

*Upper and lower 95% confidence tolerance limits established from the normal control group of 30 subjects; †denotes values that were outside the 95% confidence tolerance limit. A = late diastolic peak flow velocity; A_2D = isovolumic relaxation time (from A_2 to onset of diastolic filling); AFF = atrial filling fraction; DT = early diastolic deceleration time; E = early diastolic peak flow velocity; EF slope = rate of decline of flow velocity in early diastole; VTI-A = velocity-time integral of late diastole filling component; VTI-E = velocity-time integral of early diastole filling component.

tolerance limits established from values obtained in control subjects.

Other factors that may affect diastolic function. Heart rate did not differ between patients with sickle cell anemia and normal control subjects (RR interval 841 ± 96 vs. 864 ± 110 ms; p = NS) and also was similar in subgroups of patients with sickle cell anemia demonstrating the three patterns of diastolic filling (restrictive, impaired relaxation and normal). Systemic blood pressure was lower in patients with sickle cell anemia than in normal control subjects (Table 1); blood pressure did not differ among the patient subgroups with the three different patterns of diastolic filling. Moreover, comparisons among patients with normal versus abnormal left ventricular diastolic filling patterns showed no differences with regard to age, gender, hemoglobin level, electrophoretic pattern or cardiac dimensions (left ventricular cavity dimension, wall thickness and mass). The patient with sickle cell anemia who had received a large number of blood transfusions (i.e., up to 54) demonstrated a normal pattern of diastolic filling.

Discussion

Cardiomyopathy in sickle cell anemia. The issue of whether a cardiomyopathy (or "myocardial component") is part of the disease spectrum of sickle cell anemia has been controversial (1–4,21,22). Considerations regarding a sickle cell cardiomyopathy have arisen largely because patients often show clinical manifestations of important cardiac involvement such as exertional dyspnea, fatigue and signs of heart failure (1–6). It has been suggested (3,7) that cardiac dysfunction and failure in sickle cell anemia may result from myocardial necrosis (and replacement fibrosis) secondary to intravascular sickling of the abnormal erythrocytes within coronary artery lumens. Although there have been a few isolated reports (23,24) of myocardial infarction in patients with sickle cell anemia, this phenomenon appears to be rather uncommon and an unlikely explanation for cardiac symptoms in the vast majority of patients with this disease (25).

Left ventricular function. It has been suggested that the heart is affected as part of the disease process in patients with sickle cell anemia as a result of the chronic left ventricular volume overload and sustained high cardiac output caused by severe long-standing anemia (26). However, previous investigations (9–14) have consistently failed to show important impairment of systolic performance in patients with sickle cell anemia.

In the absence of convincing evidence for left ventricular systolic dysfunction, abnormalities of diastolic performance have been proposed as an alternative explanation for cardiac symptoms in sickle cell anemia. Utilizing digitized M-mode echocardiography to study patients with sickle cell anemia, Balfour et al. (15) showed evidence of diastolic dysfunction consisting of reduced rate of change in left ventricular cavity diastolic dimension and posterior wall thinning in patients

with sickle cell anemia compared with normal control subjects. These authors (15) suggested that in some of their patients diastolic filling abnormalities might be responsible for exercise intolerance and failure of the left ventricular ejection fraction to increase appropriately during exercise.

Patterns of diastolic filling. In this investigation, we used Doppler echocardiography to assess left ventricular diastolic filling and found that a substantial proportion of our patients with sickle cell anemia (but without overt cardiac symptoms) had evidence of abnormal indexes of diastolic filling. More than one half of our patients showed Doppler waveform alterations similar to those previously observed in patients with a variety of cardiac diseases (27–33). Specifically, two patterns of abnormal left ventricular filling were evident. In 20% of the patients, Doppler waveforms showed an abrupt and premature decrease of early diastolic flow velocity characterized by shortened deceleration time and increased rate of decline. This pattern of left ventricular filling has been described in patients with restrictive cardiomyopathies (20) including amyloidosis (31), thalassemia major (32) or rejection of a cardiac allograft (28,33), and it appears to be associated with reduced myocardial compliance and restrictive physiology (20,28). The premature decrease in early diastolic flow velocity most likely reflects a more rapid equalization of the diastolic atrioventricular (AV) pressure gradient that occurs as a consequence of abrupt increases in left ventricular pressure in early diastole. Although most previous investigations (28,31) have observed this filling pattern in patients with advanced cardiac disease, other patients with restrictive left ventricular filling have been reported to have only mild or no symptoms (32,33).

Another 35% of our patients showed a different abnormality of left ventricular diastolic filling in which the early diastolic flow velocity deceleration time was prolonged or the rate of decline of flow velocity was decreased, or both. Similar patterns of impairment in early diastolic filling have been reported previously in patients with a variety of diseases known to be associated with impaired left ventricular relaxation or reduced compliance, including coronary artery disease (27,28,34), systemic hypertension (29) and hypertrophic cardiomyopathy (30,35,36).

Factors influencing diastolic filling. The appearance of the transmitral flow velocity waveform may be influenced by factors other than intrinsic myocardial properties, including heart rate and left ventricular preload and afterload that affect the AV pressure gradient at the time of mitral valve opening (28,37,38). However, there is substantial evidence in our study patients that the abnormal Doppler findings identified were not due solely to these variables.

First, although heart rate is often increased in anemic states, none of our study patients with sickle cell anemia manifested tachycardia at the time of their Doppler study nor was heart rate different in patients with sickle cell anemia compared with normal control subjects.

Second, the restrictive filling pattern (with decreased deceleration time) identified in six of our patients with sickle cell anemia would not appear to be solely a manifestation of altered left ventricular preload. Although increased preload, which may have been present in our patients with sickle cell anemia, can itself reduce early diastolic deceleration time, this is also usually associated with an increase in early diastolic peak flow velocity (38); also, late diastolic flow velocity is increased or unchanged. In contrast, our six patients with restrictive filling pattern demonstrated normal early diastolic peak flow velocity and decreased late diastolic filling. The potential effect of increased preload in our patients with sickle cell anemia is also relevant to identification of the Doppler filling pattern of impaired relaxation. Because increased preload would probably have the effect of masking abnormalities of impaired relaxation, it is possible that we have underestimated the frequency with which diastolic relaxation abnormalities occurred in our study patients with sickle cell anemia.

Third, alterations in left ventricular afterload could not explain the abnormalities of diastolic filling observed in our patients with sickle cell anemia. Although increased afterload (or systemic blood pressure) may result in impaired early left ventricular relaxation (39), each patient with sickle cell anemia was normotensive at the time of the Doppler examination.

Limitations. Because of the noninvasive nature of the present study, left ventricular relaxation and compliance were not directly assessed and consequently we cannot be certain that the alterations of left ventricular filling we observed were solely attributable to abnormalities of the intrinsic properties of cardiac muscle. However, because extrinsic factors such as heart rate, preload and afterload appeared to have relatively small influences on the appearance of the transmitral flow velocity waveforms in the study patients, we believe it is reasonable to infer from our data that the observed alterations in Doppler diastolic indexes suggest the presence of an intrinsic myocardial abnormality.

Conclusions. The results of this investigation demonstrate that left ventricular filling abnormalities are evident with Doppler echocardiography in many patients with sickle cell anemia even in the absence of symptoms of heart failure or left ventricular systolic dysfunction. Whether these abnormal diastolic filling patterns reflect a preclinical phase of cardiac disease in certain patients in whom cardiac symptoms will subsequently become clinically overt remains to be determined. Consequently, the prognostic implications of abnormal Doppler diastolic indexes in sickle cell anemia will ultimately depend on the longitudinal assessment of these patients.

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